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ORIGINAL RESEARCH

Impact of a care pathway for COPD on adherence to guidelines and hospital readmission: a cluster randomized trial

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Purpose: Current in-hospital management of exacerbations of COPD is suboptimal, and patient outcomes are poor. The primary aim of this study was to evaluate whether implementation of a care pathway (CP) for COPD improves the 6 months readmission rate. Secondary outcomes were the 30 days readmission rate, mortality, length of stay and adherence to guidelines.

Patients and methods: An international cluster randomized controlled trial was performed in Belgium, Italy and Portugal. General hospitals were randomly assigned to an intervention group where a CP was implemented or a control group where usual care was provided. The targeted population included patients with COPD exacerbation.

Results: Twenty-two hospitals were included, whereof 11 hospitals (n=174 patients) were randomized to the intervention group and 11 hospitals (n=168 patients) to the control group. The CP had no impact on the 6 months readmission rate. However, the 30 days readmission rate was significantly lower in the intervention group (9.7%; 15/155) compared to the control group (15.3%; 22/144) (odds ratio =0.427; 95% confidence interval 0.222–0.822; *P*=0.040). Performance on process indicators was significantly higher in the intervention group for 2 of 24 main indicators (8.3%).

Conclusion: The implementation of this in-hospital CP for COPD exacerbation has no impact on the 6 months readmission rate, but it significantly reduces the 30 days readmission rate.

Keywords: COPD, care pathway, readmission, quality improvement, cluster randomized controlled trial

Introduction

Exacerbations of COPD are a leading cause of hospital admissions worldwide. Thirty-five percent of COPD patients have at least 1 admission a year, with up to 30% readmitted within the 6 months after discharge.[1–3] Adequate in-hospital management is expected to reduce readmission rates.[4] Although several worldwide established guidelines are available for the management of COPD,[2,5] the current in-hospital management of COPD exacerbations is suboptimal, and outcomes with regard to readmission and mortality are poor.[6,7]

Care pathways (CPs) are widely used for optimizing adherence to guidelines and improving outcomes.[8–10] They are defined as "a complex intervention for the mutual decision making and organization of predictable care for a well-defined group of patients during a well-defined period".[11] Although COPD exacerbations are well suited to be treated in CPs, existing research on effectiveness is limited. Moreover, not one randomized study on COPD CPs has been reported up to date.[12–15] As CPs are complex interventions that induce change at different levels of the organization,

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cluster randomized controlled trials (CRCTs) should be used to study their impact.[16]

This trial is a CRCT on CP effectiveness launched by the European Pathway Association (E-P-A) in 2009.[11] The primary aim of this study was to evaluate whether implementation of a CP improves the 6 months readmission rate for patients with a COPD exacerbation. Secondary outcomes were the 30 days readmission rate, mortality, length of stay and adherence to guidelines.

Patients and methods

Study design and participants

A pragmatic CRCT[17] was conducted, and the clusters included general hospitals out of Belgium, Ireland, Italy and Portugal, where patients hospitalized for a COPD exacerbation were cared for by a multidisciplinary team. Hospitals were randomized to either an intervention group, where a CP was developed and implemented, or a control group, where usual care was provided (Figure 1). Usual care means that team members provide the same care during the study period as they were doing before implementation in the study. The study was registered as a CRCT at ClinicalTrials.gov (identifier: NCT00962468). Ethical approval was obtained on 3 levels. First, ethical approval was sought by the ethical committee of the research center at the country level. This included approval by the ethical committee of the coordinating center at Leuven University (identifier: ML5617), the National Committee of Data Protection for Portugal (6497/2011) and the ethical committee of the AOU Maggiore della Carità di Novara for Italy (625, 21/07/2011). Second, ethical approval was sought with regard to participation in the trial at the cluster level by the ethical committee of each of the participating hospitals (Table S1). Finally, individual written informed consent was obtained from all patients with regard to participation in the study and access to the patient record.

General hospitals could develop a CP when they provided written agreement to participate in the study. When hospitals were randomized into the control group, they agreed to not develop and implement a COPD CP within the time frame of the study. Eligibility criteria for patients were 1) hospital admission with COPD exacerbation as the primary diagnosis, 2) hospitalized for at least 48 hours, 3) admitted in a ward where COPD exacerbations were usually treated, 4) able to understand and read the native language and 5) provision of written informed consent. Patients could be included in the study only once, specifically at their first admission during the study period. Patients were excluded 1) if already included in another study of which the measurements could influence the measurements or outcomes of this study or 2) if they needed invasive positive pressure ventilation at admission to the hospital.[11]

Enrollment of hospitals was done by the E-P-A, in close collaboration with the national E-P-A coordinator of each country. After consent, a study coordinator was appointed in each participating hospital.[11]

Randomization and masking

Allocation concealment at team level was not possible and therefore general hospitals were stratified by country level, hospital type (teaching versus non-teaching), hospital size (<600 and ≥600 beds) and annual patient volume for COPD exacerbation (<300 patients and ≥300 patients)[18,19] and then randomly assigned to the intervention group or to the control group. The allocation sequence was computer generated by a principal investigator at the coordination center at Leuven University, using a random number list and statistical software (http://www.randomizer.org). Study coordinators and teams were informed on their allocation after randomization. To minimize the risk for testing bias, the detailed data collection protocol was sent to the study

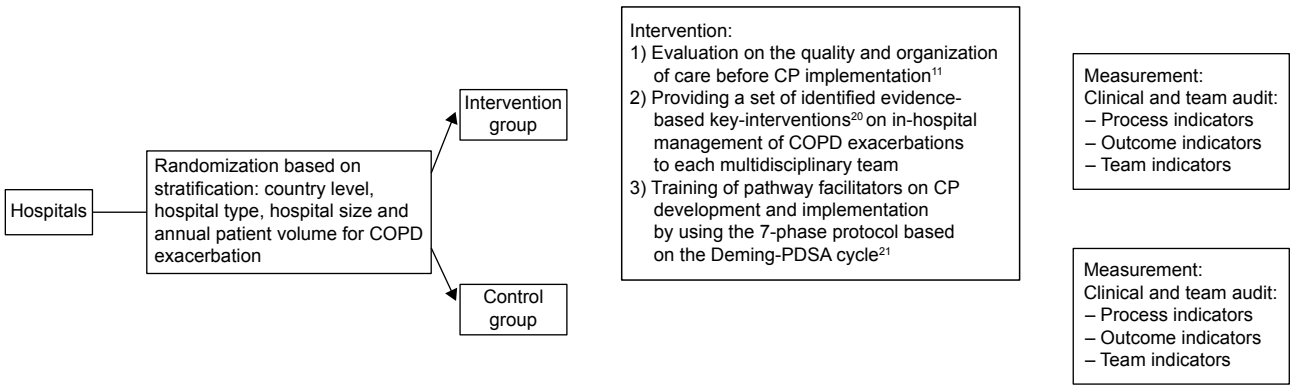

Figure 1 Study overview.
Abbreviation: CP, care pathway.

coordinator of each hospital just before the start of the data collection. Furthermore, a logbook was kept for included patients in order to be able to connect the patient identity to the study number. In addition, to check for selection bias, for each patient admitted with COPD exacerbation during the recruitment period but excluded, baseline characteristics and the reason for exclusion were reported in a logbook for excluded patients.

Finally, in order to prevent assessment bias, all data, except for the measurements at discharge, were collected by an external researcher outside the clinical team. At discharge, a structured interview of the patient by a team member was performed to collect information on previous home situation and therapy before admission, which did not imply any risk for bias of the measurements.

Intervention

In the intervention group, a CP was implemented at hospital-level CP, and the intervention was composed of 3 active components (Figure 1).[11] 1) An evaluation on the quality and organization of care before CP implementation. In every hospital, a clinical audit was performed during a 2- to 3-month period, 6 months before developing the CP. Hospitals received a feedback report describing their performance compared to evidence-based guidelines and the performance of all other participating hospitals. The purpose of this feedback report was to help the hospitals in understanding the deficiencies in their actual organization of the care. This feedback report was discussed during a workshop, held before the start of the CP development. This workshop, as part of the intervention, was held before the start of the CP development and was attended by pneumologist, (head) nurse, physiotherapists and/or pathway facilitator of each participating hospital. During this workshop, the purpose of the EQCP study was presented, and the feedback report and the key interventions were discussed. This workshop closed with the next steps of the study, and time plans were presented. 2) Providing a set of identified evidence-based key interventions[20] on in-hospital management of COPD exacerbations to each multidisciplinary team. The set of key interventions were based on literature, an international Delphi study and consensus meeting with multidisciplinary expert panel.[20] During the workshop, described earlier, these key interventions were presented and discussed. During the implementation phase, teaching sessions were organized by a pneumologist and a respiratory clinical nurse specialist concerning those key interventions for which teams experienced implementation difficulties, ie, administration of corticoid therapy, education on self-management strategies and inhalation therapy. Finally, slide kits were provided to the pathway facilitator of each hospital, ie, regarding administration of oxygen therapy, in order to support the facilitators in the education of their team members regarding the different key interventions. 3) Training of pathway facilitators on CP development and implementation by using the 7-phase protocol based on the Deming-Plan Do Study Act cycle.[21] For the development and implementation of the CP, the findings of the evaluation of the care process and the set of evidence-based key interventions were used. Meetings with the pathway facilitators were organized to further discuss the feedback reports and to address problems in implementation. Furthermore, a change expert supported change and exchange of knowledge and best practices.[11,22] The teams developed a CP over a 6- to 8-month period.[23] In the control group, patients received the usual care, and no intervention was developed or implemented before.

Measurement

The primary outcome was the 6 months readmission rate. Secondary outcomes included the 30 days readmission rate, the 30 days and the 6 months mortality rate, length of stay and results on 24 main process indicators, categorized in diagnostic, pharmacological and non-pharmacological management, respectively. Twelve of 24 main process indicators were built of 2 or more subcomponents. For the 30 days and the 6 months readmission rate, which refers to COPD-specific readmission, only patients alive at, respectively, the 30 days and the 6 months were included in the analyses.[20] Additionally, demographic and COPD-specific data were collected.

The measurement period started 2–3 months after the end of the implementation period.[21] Data were collected by structured interviews performed by a team member at discharge, patient questionnaires completed at discharge and 30 days after discharge, structured telephone interviews at 30 days and 6 months after discharge performed by the study coordinator and a patient record analysis after discharge of the patient, performed by the study coordinator, together with a clinician outside the care team. In each hospital, all data were collected centrally and subsequently provided to the national coordinators of all participating countries. Data input was performed in a central database at Leuven University and guided by using a rigorous data input protocol.

Statistical analysis

Sample size calculation was performed according to standard criteria for CRCTs.[11,24] Based on a number of 20 consecutive admitted patients in each unit, 20 hospitals needed to be included in both the intervention and the control groups.

Briefly, the intracluster correlation coefficient (ICC) for the 6 months readmission rate was estimated to be equal to 0.018, leading to a design effect of 1.342. Using standard 0.05 α error and assuming a reduction of 11% in the 6 months readmission rate (from 41% to 30%),[25,26] a sample size of 398 patients per arm was required to obtain a statistical power of 0.80.[11]

A univariate analysis was carried out testing the baseline characteristics between intervention and control groups by using the chi-square test, Mann–Whitney *U*-test and independent sample *t*-test for categorical, ordinal and continuous variables, respectively. The process indicators were analyzed by 2-level mixed-effects logistic regression model, accounting for the clustering effect. The outcome indicators are analyzed by using a 2-level mixed-effects logistic and linear regression model for categorical and continuous variables, respectively, accounting for the clustering effect. For the adjusted outcomes, the significant variables ($P<0.1$), as determined by the univariate analysis and the intervention, were included in the final model. Multicollineairity was assessed.

Statistical significance was defined as a 2-sided *P*-value of 0.05. All analyses were intention to treat, performed by using R package lme4 (version 3.1.0) and MPlus 7.3 for ICC calculations.

Results

Initially, 65 hospitals were eligible for inclusion. After receiving the detailed study protocol, 22 hospitals decided to participate in the study. Of the 43 hospitals who did not take part in the study, 26 hospitals decided to not participate because they found the workload associated with the study too high. Furthermore, all 14 Irish hospitals dropped out because of reorganization of the Irish health care system and 3 hospitals dropped out because of internal reorganization.

Regardless of the drop-out, by chance 11 hospitals were allocated to the intervention group and 11 hospitals to the control group. In total, 342 patients, 174 in the intervention group and 168 in the control group, were recruited. The Belgian hospitals included patients between October 2010 and November 2011, while the Italian and Portuguese hospitals included patients between January 2013 and April 2014. In the intervention group, respectively, 10 patients and 1 patient were lost to follow-up at 30 days and 6 months after discharge, because of not reachable by the study coordinator. In the control group, respectively, 7 and 13 patients were lost to follow-up at 30 days and 6 months after discharge for the same reason (Figure 2).

With regard to patient characteristics, the groups were highly comparable except for COPD severity at admission (higher in control group, *P*=0.018), diabetes (higher in the control group, *P*=0.007) and low body mass index (more present in the intervention group, *P*=0.003). Also, although not significant, cardiac failure and hospitalization in the year before index admission were higher in the control group. At cluster level, both groups were comparable for type, size and annual volume of patients admitted with COPD exacerbation (Table 1).

The 6 months readmission rate was lower in the intervention group (27.3%) compared to the control group (33.0%), though this result was not found statistically significant (adjusted odds ratio [OR] =0.642, 95% CI 0.347–1.188, *P*=0.158). Readmission rate at 30 days was statistically significantly lower (9.7%) in the intervention group compared to the control group (15.3%) (adjusted OR =0.427, 95% CI 0.222–0.822) (Tables 2 and 3). No significant differences were found for the 30 days and the 6 months mortality rate and length of stay.

Results on the individual process indicators are presented in Table 4. Performance on the individual process indicators was significantly higher for only 2 of 24 main indicators (8.3%) and for 9 of 41 subcomponents (22.0%). The largest differences were determined for the main indicators regarding non-pharmacological management (range of improvements: 0.7–45.9 percentage points). The mean adherence to the total of 24 measured process indicators was 59.4% (range: 18.8%–94.7%) in the intervention group and 49.4% (range: 11.8%–88.2%) in the control group (*P*=0.071). No patient received all the care they should receive.

Discussion

The implementation of this CP has no significant effect on the 6 months readmission rate. However, the 30 days readmission rate was significantly lower in the intervention group (9.7%) compared to the control group (15.3%). Performance on process indicators was significantly higher in the intervention group for 2 of 24 main indicators (8.3%) and for 9 of 41 subcomponents (22.0%).

Before the launch of this study, only 5 national CRCTs on CPs had been conducted.[23,27–30] This first international trial provides new knowledge on the design of a multicountry CRCT. In comparison to former pathway studies, 1) the impact of the CP on the care itself was comprehensively investigated, while earlier studies focused primarily on outcomes,[12–15] 2) training of teams was an active component of the intervention and 3) a clinical audit, as part of the intervention, allowed each hospital to focus on those key interventions that showed most room for improvement.[21]

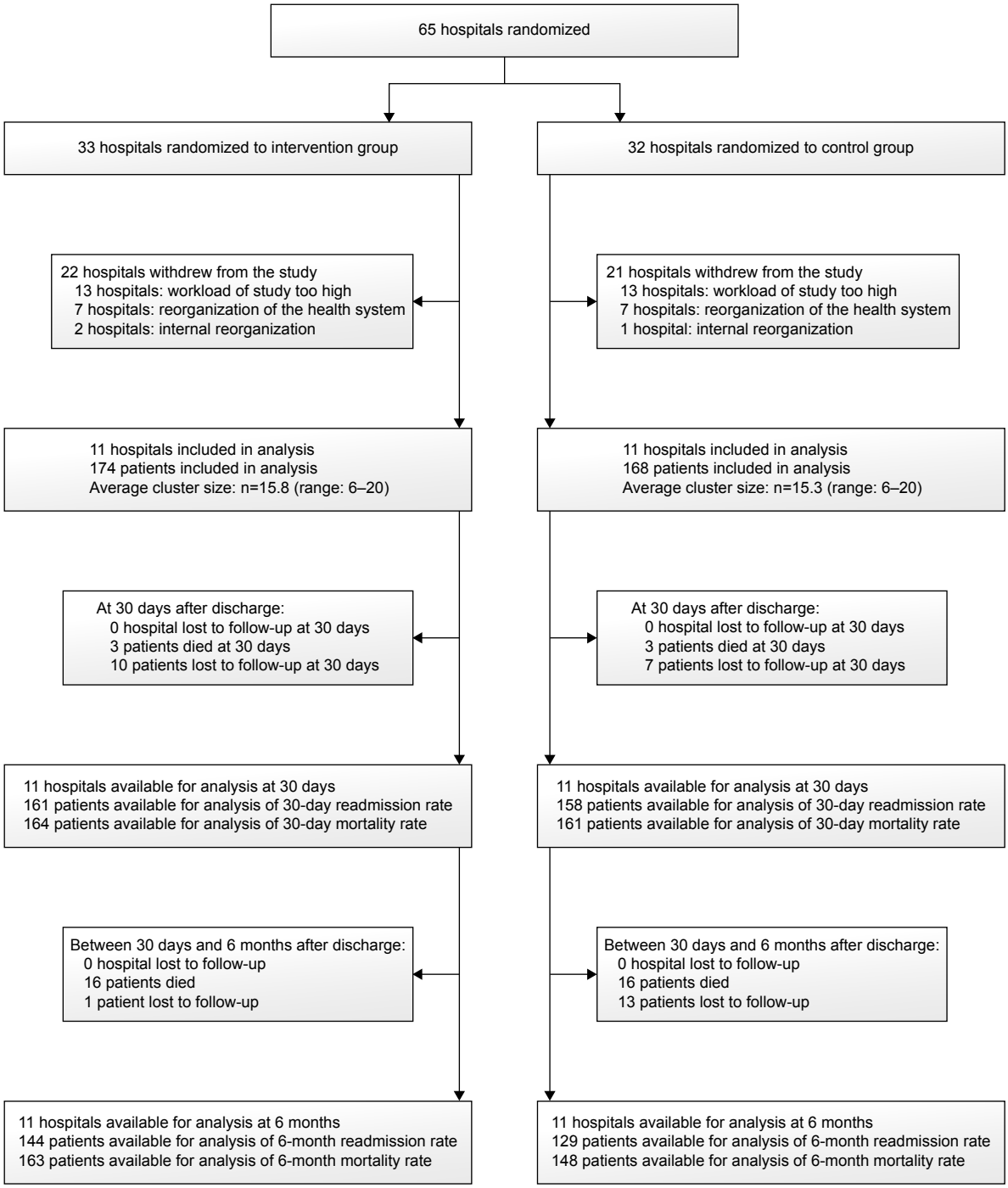

Figure 2 Participant flow at hospital and patient level.

A weakness of the study is that 43 hospitals withdrew after randomization, which resulted in a smaller sample size than initially targeted. It is reasonable to assume that the lower power of the study may have led to a failure in detecting statistically significant differences. The experience in this study is that a multicountry CRCT poses a major challenge due to standardization of the intervention in order to deliver the "same" intervention at the different sites, logistic, economic and cultural issues. These conditions should be considered carefully before starting an international CRCT. The study was underpowered, but it was decided not to increase the number of patients within the clusters because increasing the sample size per cluster does not increase power.[31]

Research on COPD CPs is very limited. Previous studies described positive effects on blood sampling, daily weight measurement, arterial blood gas measurement, referral to

Table 1 Baseline characteristics of patients and hospitals

	Intervention group (n=174)	Control group (n=168)	*P*-value[a]
Individual level			
Age (years)	69.4 (10.8)	70.4 (9.7)	0.337
Gender			0.645
Men	116/174 (66.7)	116/168 (69.0)	
Women	58/174 (33.3)	52/168 (31.0)	
COPD severity at admission			0.018
GOLD I: mild	8/171 (4.7)	12/154 (7.8)	
GOLD II: moderate	55/171 (32.2)	29/154 (18.8)	
GOLD III: severe	68/171 (39.8)	57/154 (37.0)	
GOLD IV: very severe	40/171 (23.4)	56/154 (36.4)	
Unknown	3	14	
Smoking status			0.879
No smoker	11/171 (6.4)	13/168 (7.7)	
Ex-smoker	87/171 (50.9)	86/168 (51.2)	
Active smoker	73/171 (42.7)	69/168 (41.1)	
Unknown	3	0	
Hospitalization in the year before index admission[b]			0.234
0	101/154 (65.6)	85/145 (58.6)	
≥1	53/154 (34.4)	60/145 (41.4)	
Unknown	20	23	
Charlson comorbidity index			0.160
≤2	59/174 (33.9)	45/168 (26.8)	
>2	115/174 (66.1)	123/168 (73.2)	
Cardiac failure[c]	56/171 (32.7)	69/165 (41.8)	0.091
Unknown	3	3	
Diabetes[d]	21/171 (12.3)	39/165 (23.6)	0.007
Unknown	3	3	
BMI			
<20	46/159 (28.9)	23/156 (14.7)	
≥20	113/159 (71.1)	133/156 (85.3)	0.003
Unknown	15	12	
Hospital level			
Teaching hospitals	5/11 (45.5)	5/11 (45.5)	1.000
>600 beds	2/11 (18.2)	3/11 (27.3)	0.610
>300 patients admitted with COPD exacerbation per year	2/11 (18.2)	1/11 (9.1)	0.531

Notes: Data are mean (SD) or n/N (%). [a]Chi-square test, Mann–Whitney *U*-test and independent sample *t*-test for categorical, ordinal and continuous variables, respectively. [b]Index admission: first admission during the study, at point of inclusion. [c]Includes heart failure, arrhythmia, valvular disease, acute myocardial infarction and ischemic heart disease. [d]Includes diabetes uncomplicated and complicated.

Abbreviations: BMI, body mass index; GOLD, Global Initiative for Obstructive Lung Disease; SD, standard deviation.

Table 2 Results on outcome indicators

	Intervention group	Control group	Difference unadjusted			Difference adjusted	
			OR (95% CI)	*P*-value	ICC	OR (95% CI)	*P*-value
6 months readmission	38/139 (27.3)	38/115 (33.0)	0.817 (0.454–1.470)	0.500	0.015	0.642 (0.347–1.188)	0.158
30 days readmission	15/155 (9.7)	22/144 (15.3)	0.570 (0.223–1.450)	0.241	0.041	0.427 (0.222–0.822)	0.040
6 months mortality	18/157 (11.5)	18/134 (13.4)	0.822 (0.314–2.157)	0.691	0.065	0.611 (0.189–1.972)	0.410
30 days mortality	3/168 (1.8)	2/153 (1.3)	0.965 (0.192–4.840)	0.965	NC	0.880 (0.126–6.166)	0.898
Length of stay	12.0 (10.5)	12.8 (12.4)	0.550 (0.021–14.284)	0.720	0.043	0.901 (0.015–53.049)	0.960

Notes: Adjusted for COPD severity at admission, cardiac failure, diabetes, BMI and intervention–control group.

Abbreviations: BMI, body mass index; 95% CI, 95% confidence interval; ICC, intracluster correlation coefficient; NC, not possible to calculate; OR, odds ratio.

Table 3 Two-level mixed-effects regression model

	6 months readmission		30 days readmission	
	OR (95% CI)	***P*-value**	**OR (95% CI)**	***P*-value**
COPD severity at admission				
GOLD I	1.0 (Reference)	–	1.0 (Reference)	–
GOLD II	0.652 (0.155–2.746)	0.560	0.304 (0.067–1.394)	0.252
GOLD III	0.724 (0.183–2.867)	0.645	0.220 (0.051–0.941)	0.041
GOLD IV	0.834 (0.204–3.408)	0.801	0.337 (0.079–1.436)	0.141
Cardiac failure	1.236 (0.655–2.333)	0.513	1.149 (0.511–2.580)	0.737
Diabetes	0.945 (0.395–2.259)	0.898	1.508 (0.540–4.210)	0.433
BMI	0.714 (0.363–1.405)	0.300	0.697 (0.289–1.686)	0.424
Main effect adjusted for (intervention–control group)	0.642 (0.347–1.188)	0.158	0.427 (0.222–0.822)	0.040

Abbreviations: BMI, body mass index; 95% CI, 95% confidence interval; GOLD, Global Initiative for Chronic Obstructive Lung Disease; OR, odds ratio.

Table 4 Results on process indicators: main level and subcomponent level[a]

	Intervention group, n/N (%)	**Control group, n/N (%)**	***P*-value**	**Difference between intervention and control group**
Process indicators on diagnostic management				
1. Performance of ABG measurement during first 24 hours of admission	136/174 (78.2)	126/168 (75.0)	0.526	3.2
2. Performance of chest X-ray during first 24 hours of admission	160/174 (92.0)	143/168 (85.1)	0.773	6.9
a. Performance of chest X-ray during hospitalization	172/174 (98.9)	164/168 (97.6)	0.445	1.3
b. Performance occurred within first 24 hours of admission	160/172 (93.0)	143/164 (87.2)	0.895	5.8
3. Performance of electrocardiogram during first 24 hours of admission	134/174 (77.0)	121/168 (72.0)	0.847	5.0
a. Performance of electrocardiogram during hospitalization	161/174 (92.5)	149/168 (88.7)	0.442	3.8
b. Performance occurred within first 24 hours of admission	134/161 (83.2)	121/149 (81.2)	0.867	2.0
4. Sputum culture and antibiogram in patients with purulent sputum and/or before starting antibiotics	110/154 (71.4)	88/151 (58.3)	0.626	13.1
5. Measurement of FEV_1 during current hospitalization	123/174 (70.7)	102/168 (60.7)	0.248	10.0
Process indicators on pharmacological management				
6. Prescription of short-acting bronchodilators during hospitalization	160/174 (92.0)	113/168 (67.3)	0.116	24.7
7. Prescription of long-acting bronchodilators during hospitalization	139/174 (79.9)	139/168 (82.7)	0.606	–2.8
8. Prescription of 30–40 mg of oral prednisolone daily for 7–10 days	50/174 (28.7)	19/168 (11.3)	0.091	17.4
a. **Systemic glucocorticosteroids prescribed during hospitalization**	**152/174 (87.4)**	**135/168 (80.4)**	**<0.001**	**7.0**
b. Prescription of glucocorticosteroids for 7 days to maximum 14 days starting at admission in patients in which glucocorticoids were prescribed	113/152 (74.3)	83/135 (61.5)	0.203	12.8
c. **Dose of glucocorticosteroids prescribed during first 7 days of hospitalization was 30–40 mg in patients in which glucocorticoids were prescribed**	**134/152 (88.2)**	**93/135 (68.9)**	**0.022**	**19.3**
d. Oral administration since hospitalization day 2 or earlier in patients in which glucocorticoids were prescribed	80/152 (52.6)	43/135 (31.9)	0.312	20.7
9. Prescription of antibiotics	139/174 (79.9)	139/168 (82.7)	0.655	–2.8
Process indicators on non-pharmacological management				
10. Administration of controlled oxygen therapy in patients hypoxemic during admission	44/47 (93.6)	39/42 (92.9)	0.996	0.7
11. Assessment of smoking status	161/174 (92.5)	153/168 (91.1)	0.970	1.4
12. Smoking cessation intervention in active smokers at admission	3/42 (7.1)	0/40 (0.0)	NC	7.1
a. **Providing of spoken information about quitting strategies by physician or nurse in active smokers at admission**	**23/42 (54.8)**	**10/40 (25.0)**	**0.030**	**29.8**
b. **Providing of smoking cessation leaflet in active smokers at admission**	**15/42 (35.7)**	**1/40 (2.5)**	**0.049**	**33.2**

(*Continued*)

Table 4 (*Continued*)

	Intervention group, n/N (%)	Control group, n/N (%)	*P*-value	Difference between intervention and control group[a]
c. Providing of quitting aids before discharge in active smokers at admission who wants to quit smoking by using quitting aids (patches, gum, medication)	9/16 (56.3)	3/9 (33.3)	0.277	23.0
d. Referral to counseling in active smokers at admission who wants to quit smoking by counseling (individual/group)	2/3 (66.7)	1/4 (25.0)	0.880	41.7
e. Contacting of patient in the following month after discharge by the general practitioner, primary nurse or somebody of the hospital about his/her smoking or attempt to quit in active smokers at admission	6/42 (14.3)	4/40 (10.0)	0.726	4.3
13. **Adequate education regarding inhaler therapy in patients in which inhaler therapy is prescribed**	**61/173 (35.3)**	**15/165 (9.1)**	**0.037**	**26.2**
a. Providing of education regarding inhaler medication in patients in which inhaler therapy is prescribed	110/173 (63.6)	33/165 (20.0)	0.118	43.6
b. **Providing of education regarding inhaler technique in patients in which inhaler therapy is prescribed**	**114/173 (65.9)**	**33/165 (20.0)**	**0.049**	**45.9**
c. Providing of education regarding inhaler device in patients in which inhaler therapy is prescribed	109/173 (63.0)	37/165 (22.4)	0.171	40.6
d. Providing of a leaflet with explanation regarding inhaler therapy in patients in which inhaler therapy is prescribed	81/170 (47.6)	53/162 (32.7)	0.192	14.9
14. Education regarding home oxygen therapy in patients in which home oxygen is prescribed	14/52 (26.9)	0/64 (0.0)	NC	26.9
a. Providing of education regarding oxygen source in patients in which home oxygen is prescribed	25/52 (48.1)	15/64 (23.4)	0.374	24.7
b. Providing of education regarding equipment (cannulae/mask) in patients in which home oxygen is prescribed	24/52 (46.2)	13/64 (20.3)	0.414	25.9
c. Providing of education regarding safety precautions in patients in which home oxygen is prescribed	24/52 (46.2)	8/64 (12.5)	0.481	33.7
d. Providing of spoken information regarding oxygen therapy in patients in which home oxygen is prescribed	25/50 (50.0)	16/62 (25.8)	0.241	24.2
e. Providing of a leaflet with explanation regarding oxygen therapy in patients in which home oxygen is prescribed	18/50 (36.0)	12/62 (19.4)	0.219	16.6
15. Performance of revalidation tests during the past year (inclusive current hospitalization)	20/174 (11.5)	13/168 (7.7)	0.493	3.8
16. Referral to pulmonary revalidation during the past year	76/174 (43.7)	52/168 (31.0)	0.192	12.7
17. **Nutritional assessment (BMI)**	**111/174 (63.8)**	**30/168 (17.9)**	**0.002**	**45.9**
18. Nutritional management in patients with underweight	10/57 (17.5)	3/38 (7.9)	0.411	9.6
a. **Referral to dietician in patients with underweight**	**27/57 (47.4)**	**5/38 (13.2)**	**0.015**	**34.2**
b. **Providing of nutritional advice in patients with underweight**	**21/57 (36.8)**	**4/38 (10.5)**	**0.040**	**26.3**
c. Providing of nutritional supplement in patients with underweight	21/57 (36.8)	8/38 (21.1)	0.354	15.7
19. Nutritional management in patients with overweight	10/28 (35.7)	4/23 (17.4)	0.443	18.3
a. Referral to dietician in patients with overweight	16/28 (57.1)	5/23 (21.7)	0.051	35.4
b. Providing of advice regarding weight loss in patients with overweight	14/28 (50.0)	6/23 (26.1)	0.372	23.9
20. Patient received influenza vaccination within the past year	113/174 (64.9)	97/168 (57.7)	0.991	7.2
21. Patient received pneumococcal vaccination within the past 5 years	66/174 (37.9)	85/168 (50.6)	0.076	−12.7
22. ABG measurement 1 or 2 days prior to discharge in patients hypoxemic during a COPD exacerbation	22/51 (43.1)	20/46 (43.5)	0.921	−0.4
23. Prescription of home oxygen therapy in patients with hypoxemia at discharge	3/5 (60.0)	4/15 (26.7)	0.566	33.3
a. Proportion of patients in which home oxygen is prescribed in patients who remain hypoxemic at discharge	3/5 (60.0)	7/15 (46.7)	0.879	13.3
b. Proportion of patients with indication for home oxygen therapy, in which home oxygen therapy was prescribed for at least 16 hours a day in patients who remain hypoxemic at discharge	3/5 (60.0)	4/15 (26.7)	0.566	33.3

(*Continued*)

Table 4 (*Continued*)

	Intervention group, n/N (%)	Control group, n/N (%)	*P*-value	Difference between intervention and control group[a]
24. Adequate discharge management	51/174 (29.3)	26/168 (15.5)	0.330	13.8
a. Assessment of residence during current hospitalization	169/174 (97.1)	151/168 (89.9)	0.862	7.2
b. Assessment of residential status within 3 days at admission	151/169 (89.3)	129/151 (85.4)	0.940	3.9
c. Assessment of living status during current hospitalization	150/174 (86.2)	149/168 (88.7)	0.228	–2.5
d. Assessment of living status within 3 days of admission	122/150 (81.3)	128/149 (85.9)	0.289	–4.6
e. Assessment of social status during current hospitalization	153/174 (87.9)	145/168 (86.3)	0.501	1.6
f. Assessment of social support within 3 days	115/153 (75.2)	124/145 (85.5)	0.199	–10.3
g. Providing of spoken explanation about home medication	88/174 (50.6)	78/167 (46.7)	0.855	3.9
h. Providing of discharge letter with explanation about further medication after discharge	100/174 (57.5)	83/167 (49.7)	0.473	7.8
i. Providing of letter with information about follow-up appointment	91/174 (52.3)	63/167 (37.7)	0.276	14.6
j. **Planning of follow-up appointment at 4–6 weeks after discharge**	**151/174 (86.8)**	**95/167 (56.9)**	**<0.001**	**29.9**
k. Availability of letter for general practitioner in medical record	171/174 (98.3)	161/168 (95.8)	0.314	2.5
l. **Support arranged at discharge if needed**	**25/32 (78.1)**	**10/23 (43.5)**	**<0.001**	**34.6**
Prescription of nebulizer at the day of discharge	63/174 (36.2)	67/168 (39.9)	0.898	–3.7

Note: [a]Results in bold refer to significance.
Abbreviations: ABG, arterial blood gas; BMI, body mass index; FEV_1, forced expiratory volume at 1 second; NC, not possible to calculate.

rehabilitation, feelings of anxiety, readmission and in-hospital mortality. Due to limited statistical analysis and weak study design, the internal validity of results is limited.[12–15] Our study confirmed that the implementation of a CP significantly reduces the 30 days readmission rate.[32,33]

Although the 30 days readmission rate was significantly lower in the intervention group, no differences were found for readmission rate at 6 months. The 6 months readmission was chosen as primary outcome, based on previous studies and expert opinion. However, during the study, it became clear that the outcomes at 30 days after discharge are highly associated with the in-hospital treatment, which was the focus of the CP intervention, while results at 6 months are mainly related to the nature of the disease and the quality of the outpatient and primary care. Therefore, for future studies on in-hospital CPs and readmission, it is recommendable to primarily focus on the 30 days readmission.[2] Finally, according to our results, ~6 of every 100 COPD patients treated according to the CP avoid a readmission at 30 days (number needed to treat: 17.0). Worldwide, based on the data of the WHO, this would result in a potential reduction of ~4 million readmissions.[34]

With regard to process indicators, only 2 of these results were statistically significant, and by implementing a CP, the mean adherence to the guidelines was higher in the intervention group compared to the control group, though this difference was not significant. However, even non-significant results on process indicators may provide valid information regarding quality of care. Indeed, existing clinical practice guidelines on management of COPD exacerbation, which are very congruent and continuously updated, recommend unambiguously that the evaluated processes should be performed in every patient who is hospitalized for COPD exacerbation, regardless of patient characteristics or contextual factors. It is important to notice that, despite large improvements on process indicators after CP implementation, a considerable number of processes, especially with regard to non-pharmacological management, remained suboptimal performed. The non-pharmacological management contains some key interventions regarding education concerning smoking cessation, inhaler therapy and home oxygen therapy. Guidelines recommend more education as education is seen as an important part in the treatment of patients with a COPD exacerbation.[2] After implementing the CP, performance of education regarding inhaler therapy was significantly improved (9.1% in the control group and 35.3% in the intervention group; Table 4). Although only 35.3% of the patients received education regarding inhaler therapy, while the other process indicators regarding education were even performed lower. So the care for patients with a COPD exacerbation is suboptimal performed, and therefore, continuous quality improvement will be needed in order to further optimize the care process for in-hospital management of COPD exacerbation and to enhance sustainability of the improved results.[35,36] In addition, it is recommended that the team reconsiders the content of the pathway every 6 months.[21] For instance, at the

beginning of 2014, the evidence concerning optimal duration of glucocorticoid therapy for acute exacerbations of COPD was changed.[2,37]

Follow-up research is needed to understand why and under which circumstances CPs work in terms of which active components in CPs underlie their effect and what is the role of contextual factors and multidisciplinary teamwork. Furthermore, an economic evaluation should be included to evaluate whether CPs also impact efficiency of care. Finally, in the context of the rising prevalence of COPD, CPs should also include transmural management and community-based treatment of COPD.[2]

Conclusion

The implementation of this in-hospital CP for COPD exacerbation significantly reduced the 30 days readmission rate. This first international cluster randomized trial on CPs shows that the evidence-based key interventions are better performed after implementation of a CP compared to usual care. Additional studies are needed to understand how CPs are working, what their effect is on long term and how they affect the organization of care for different patient groups.

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Supplementary material

Table S1 List of participating hospitals that gave ethical approval for this study

ASL AT
AO Mauriziano di Torino
AOU Maggiore della Carità di Novara ward 1
AOU Maggiore della Carità di Novara ward 2
AOU San Luigi di Orbassano
ASL AL
ASL TO1
ASL VC
AZ Sint – Augustinus Wilrijk
AZ Sint Elizabeth Zottegem
AZ Sint-Blasius Dendermonde
AZ Sint-Jan AV Brugge
Centro Hospitalar Lisboa Central
Heilig Hart ziekenhuis Roeselare – Menen campus Menen
Heilig Hart ziekenhuis Roeselare Menen campus Roeselare
Hospital Distrital de Faro
Mariaziekenhuis Overpelt
RZ Jan Yperman Ieper
Sint-Elisabeth Ziekenhuis Turnhout
Sint-Vincentius ziekenhuis, Antwerpen
Virga Jesse Ziekenhuis Hasselt
ZiekenhuisNetwerk Antwerpen campus Jan Palfijn

Abbreviations: ASL AT, Azienda Sanitaria Locale di Asti; AO, Azienda Ospedaliera; AOU, Azienda Ospedaliero Universitaria; ASL AL, Azienda Sanitaria Locale della provincia di Alessandria; ASL VC, Azienda Sanitaria Locale di Vercelli; ASL TOI, Azienda Sanitaria Locale Torino; AZ, Algemeen ziekenhuis; RZ, Regionaal ziekenhuis.